REMARKS

Claims 33 and 97-100 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1-3. Applicants note that the amendments of paper #11 have obviated the restriction requirement. Claims 42, 43, and 50-96 have been cancelled. Claims 33 and 97-100 are currently under examination.

4. Applicants note with appreciation that the petition filed under 37 CFR 1.48(b) for the removal of inventors Lou L. Houston and David B. Ring has been accepted.

5. Applicants enclose herewith a copy of the references cited in the IDS filed 5/30/00.

6. The disclosure is objected to for allegedly containing the following informalities.

a. Applicants have amended the specification, as requested, to provide the correct lineage to related applications. Applicants' correction of the disclosure obviates the objection.

b. The Office Action alleges that Applicants' incorporation of subject matter by reference to U.S. Patent 5,091,513 is improper. Applicants traverse this objection.

First, the Examiner confuses two situations: a) cases in which the intent to incorporate a document was at issue; with b) cases in which it is agreed that there was an intent to incorporate the document. The intent to incorporate U.S. 5,091,513 in this case is clear, and the examiner does not argue otherwise. So all agree that applicants evidenced an intent to incorporate that patent **in its entirety**.

The Office Action asserts that the incorporation is improper, because the recitation in the specification allegedly does not point to a specific portion of the U.S. patent from which the material was incorporated. Thus the Examiner's problem is not a failure to evidence the intent to incorporate; it is the amount of information that clearly was incorporated. The Examiner's ruling clearly implies that there is some limit to the amount of information that one can incorporate.

This patent application is already lengthy. By the examiner's reasoning, that fact by itself would create an issue under 35 U.S.C §112 ¶1 because one has to deal with a lengthy document.

Understandably, the rule the Examiner tries to create does not exist. The very reason for incorporating documents into a specification is to get control of what has become an undesirable proliferation of topics added to every specification for fear of leaving out some information that later is considered essential to satisfy under 35 U.S.C §112 ¶1. It would be perverse in the extreme to decide that the very solution to this problem is in itself improper simply because of the length of the documents being incorporated.

Applicants respectfully reiterate that the specification does not merely refer to U.S. Patent No. 5,091,513, as was true in *In re de Seversky*, cited in the Office Action. Indeed, U.S. Patent No. 5,091,513 is *expressly* incorporated by reference on page 26 of the specification as filed. "A detailed description for engineering and producing sFv proteins by recombinant means appears in U.S. Patent 5,091,513 claiming priority from U.S.S.N. 052,800, filed May 21, 1987, assigned to Creative BioMolecules Inc., hereby incorporated by reference." Applicants assert that this statement is sufficient to incorporate the *entirety* of U.S. Patent No. 5,091,513 into the specification.

Applicants respectfully direct the Examiner's attention to *Telemac Cellular v. Topp Telecom*, 247 F.3d 1316, 1329, 58 U.S.P.Q.2d 1545 (Fed. Cir. 2001), which states, "[w]hen a document is 'incorporated by reference' into a host document, such as a patent, the referenced document becomes effectively part of the host document as if it were explicitly contained therein. *Advanced Display Sys. v. Kent State,* 212 F.3d 1272, 1282, 54 USPQ2d 1673, 1679 (Fed. Cir. 2000)." Of particular note is that *the entire document* is considered to be incorporated – not merely a portion. By the Office Action's logic, such an incorporation would be an impossibility, because an entire document could not be incorporated by reference if it were required that "specific portions" be pointed out. Neither of the above cited cases in an aberration. "As the expression itself implies, the purpose of 'incorporation by reference' is to make one document become a part of another document by referring to the former in the latter in such a manner that it is apparent that the cited document is part of the referencing document as if it were fully set out therein." *Application of Lund,* 376 F.2d 982, 989 (C.C.P.A. 1967).

Other cases, should the Examiner choose to review them, reach a similar result. *Rolls Royce v. United States*, 339 F.2d 654, 168 Ct.Cl. 367 (1964); *Technograph Printed Circuits v. Bendix Aviation*, D.C., 218 F.Supp. 1, 31, aff'd 327 F.2d 497 (4 Cir., 1964); *B. F. Goodrich v. U.S. Rubber*, D.C., 147 F.Supp. 40, 58, [FN11] aff'd 244 F.2d 468 (4 Cir., 1957).

Indeed, courts of appeals feel strongly about this issue: "Filing cabinets abhor redundancy. Warehouses covet their space. The overcrowded conditions of offices in this city are in direct ratio to the space needed for storing of documents. The Patent Office was conceived by a document and has been prolific in that regard from its inception. These considerations warrant an economizing of words so as to alleviate these serious conditions. We do not feel that this economy will be at the expense of clarity and thereby frustrate the effectiveness of the statute." *General Elec. Co. v. Brenner*, 407 F.2d 1258, 1263 (D.C. Cir. 1968).

In summary, Applicants submit that there is no legal basis for the Office Action's assertion that only a portion of a public document can be incorporated by reference, and that any such portion must be explicitly pointed out. This conclusion is underscored by the apparent lack of any case law indicating that the words "incorporated by reference" are not themselves sufficient to effect the legal incorporation. Reconsideration and withdrawal of this objection are respectfully requested.

7. Claims 33 and 100 are objected to due to informalities. Specifically, claim 33 is objected to for containing a typographical error. Applicants have amended claim 33 to correct the typographical error obviating the objection. Additionally, claim 100 is objected to for being a substantial duplicate of claim 98. Applicants have amended claim 100 to distinguish the claimed subject matter from that of claim 98. Accordingly, reconsideration and withdrawal of the objection is requested.

8-9. Claims 33-100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. To expedite prosecution, Applicants have amended the claims to incorporate the Examiner's suggestions. Such amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection is requested.

a. Claims 33-100 are rejected due to lack of clarity in the language. Applicants amendments to claim 33 obviate this rejection. Applicants point out that the amendment was made solely to improve the clarity of the language, and does not narrow the scope of the claim.

b. Claims 97-100 are rejected for the alleged ambiguity in the recitation of "derived". To expedite prosecution, Applicants have amended the claims to delete "derived" obviating the rejection.

c. Claims 98 and 100 are rejected due to lack of clarity in the language. Applicants have amended the claims to improve their clarity, thus obviating the rejection. Applicants point out that the amendment was made solely to improve the clarity of the language, and does not narrow the scope of the claim.

10-11. Claims 33 and 97-100 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection, as it is based entirely on an improper application of incorporation-by-reference doctrine, as discussed in detail above.

Support for the claimed subject matter can be found in the specification, as filed 10/01/01, on page 4, line 1-page 7, line 23. To illustrate how these passages provide adequate written description of the claimed subject matter, Applicants specifically draw the Examiner's attention to page 4, lines 7-10; page 4, lines 16-19; page 4, lines 22-26; and page 5, lines 1-6.

AFTER INCORPORATION

PAGE 6 NOT 4

> "In its broadest aspects, this invention features polypeptides comprising biosynthetic antibody binding sites, DNA encoding these polypeptides prepared by recombinant DNA techniques, vectors comprising these DNAs, and methods for the production of these polypeptides." (page 4, lines 7-10).
>
> "It has now been discovered that framework regions from diverse species are effective to maintain CDRs from diverse other species in proper conformation so as to achieve true immunochemical binding properties in a biosynthetic protein." (page 4, lines 16-19).

> "The structure of these synthetic polypeptides is unlike that of naturally occurring antibodies, fragments thereof, or known synthetic polypeptides or "chimeric antibodies" in that the regions of the BABS responsible for specificity and affinity of binding, (analogous to native antibody variable regions) are themselves chimeric, e.g., comprise amino acid sequences homologous to portions of at least two different antibody molecules." (page 4, lines 22-26).
>
> "[T]he chimeric polypeptides comprise an amino acid sequence homologous to at least a portion of the variable regions of a mammalian immunoglobulin, such as those of mouse, rat, or human origin. In one preferred embodiment, the biosynthetic antibody binding site comprises FRs homologous with a portion of the FRs of a human immunoglobulin and CDRs homologous with CDRs from a mouse immunoglobulin." (page 5, lines 1-6).

Additionally, support for methods of making the claimed polypeptides can be found on page 26, line 10-page 27, line 27.

However, Applicants' citation of passages of the specification incorporated-by-reference in the response filed 10/01/01 is by no means in acquiescence of the Examiner's contention that the specification as originally filed failed to provide adequate written description for the claimed subject matter. Applicants direct the Examiner's attention to the marked-up version of the specification filed 10/01/01, and note that the following passages were also found in the specification as originally filed: page 10, lines 2-8; page 10, lines 20-29; and page 14, line 25-page 15, line 2. These passages illustrate that the specification satisfies the written description requirement, both with subject matter explicitly stated and with subject matter incorporated-by-reference. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

12. Claims 98 and 100 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action alleges that Applicants have failed to provide enablement for polypeptides wherein some of the CDRs are from human immunoglobulin sequences. Applicants traverse this rejection.

The Examiner is reminded that in accordance with MPEP 2164.06, the fact that the amount of experimentation required is extensive or time consuming does not make such experimentation undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). "An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Applicants point out that, in accordance with MPEP 2164.02, the standard for enablement is not whether Applicant has reduced the invention to practice prior to the filing date. "An example may be working or prophetic. A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." (MPEP 2164.02). Rather the standard for enablement is whether one of skill in the art could practice the claimed invention using Applicants disclosure in light of that which is known in the art. Applicants contend that the present disclosure satisfies this criteria.

Applicants point out that the specification provides ample support describing the chimeric single chain antibodies of the present invention, and methods to make such chimeric single chain antibodies (see, for example, page 25, lines 20-22; page 25, line 23-page 26, line 9). The specification additionally points out that "it has now been discovered that framework regions from diverse species are effective to maintain CDRs from diverse other species in proper conformation so as to achieve true immunochemical binding properties in a biosynthetic protein." (page 4, line 16-19). Furthermore, "the structure of these biosynthetic polypeptides is unlike that of naturally occurring antibodies, fragments thereof, or known synthetic polypeptides or "chimeric antibodies" in that the regions of the BABS responsible for specificity and affinity of binding, (analogous to native antibody variable regions) are themselves chimeric, e.g., comprise amino acid sequences homologous to portions of at least two different antibody molecules." (page 4, lines 22-26).

Applicants point out that the claims are specifically directed to a "single polypeptide chain in which said framework and complementarity determining regions together define a variable region binding domain which can be immunologically reactive with an antigen." Accordingly, the claims specifically exclude from their scope embodiments which do not form a functional antigen binding region, and one of skill in the art can readily identify the claimed subject matter. This is the standard under MPEP 2164.08(b), which states that "[t]he presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." Accordingly, Applicants contend that the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection is requested.

13-14. Claims 33, 97, and 99 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 and 9-12 of U.S. Patent No. 5091513 in view of Jones et al. (1986). Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

15-16. Claims 33, 97, and 99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klausner et al. and further in view of Pastan et al. and Jones et al. Applicants traverse this rejection.

The Examiner is reminded that, in accordance with MPEP 2143, three criteria must be met to establish a case of prima facie obviousness: "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." Contrary to the assertions of the prior Office Action, Applicants contend that the cited references fail to meet at best two of the three criteria, and as such fail to establish a prima facie case of obviousness. Specifically, the

cited references fail to teach each and every claim limitation, and fail to provide a reasonable expectation of success.

First and foremost, Applicants point out that the cited references, even when combined, fail to teach each and every limitation of the pending claims. Most notably, the pending claims are directed to an isolated polypeptide including an antigen binding site, comprising "(b) an amino acid sequence that is part of said single polypeptide chain, and has a biological activity independent of said immunological reactivity." Applicants point out that the claims are directed not to a single chain antibody cross-linked or coupled to an additional moiety such as an immunotoxin or targeting moiety, but to a single chain antibody wherein such additional moiety is a part of said single polypeptide chain. Although the teachings of Klausner et al. suggest the desirability of targeting single chain antibodies, and Pastan et al. teach cross-linking a toxin to an antibody (Applicants point out that this antibody is not a single chain antibody), Pastan et al. fails to teach chimeric single chain antibodies wherein additional moieties are part of said single chain polypeptide. Accordingly, absent Applicants' disclosure, one of skill in the art would not have a reasonable expectation of success in generating single chain polypeptides that meet each and every limitation of the claimed subject matter.

Applicants remind the Examiner that in accordance with MPEP 2112, "[T]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."

> "In re Rijckaert, 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency, however, may not be established by probabilities or possibilities** (emphasis added). The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient.' In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed Cir. 1999) (MPEP 2112)

For these reasons, Applicants contend that the Office Action fails to establish a prima facie case of obviousness. The cited references fail to teach or suggest each and every limitation

of the claims. Furthermore, in view of the cited references alone and without benefit of Applicants' disclosure, one of skill in the art could not have practiced the claimed invention with a reasonable expectation of success. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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